OAR Box 1192

Prepped by Candice Davis

Document Number:

132) IV-D-194

Docket Number:

A-90-16

A-90-16
IV-D-194

HUNTON & WILLIAMS

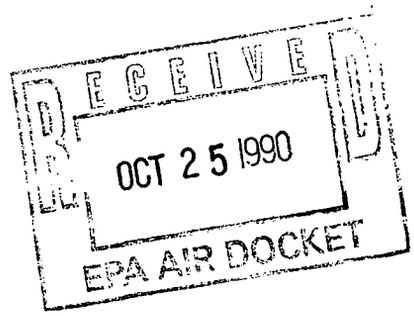
ATLANTA, GEORGIA
BRUSSELS, BELGIUM
FAIRFAX, VIRGINIA
KNOXVILLE, TENNESSEE

P. O. BOX 19230
2000 PENNSYLVANIA AVENUE, N.W.
WASHINGTON, D.C. 20036
TELEPHONE (202) 955-1500
FAX (202) 778-2201

NEW YORK, NEW YORK
NORFOLK, VIRGINIA
RALEIGH, NORTH CAROLINA
RICHMOND, VIRGINIA

FILE NO.: 23390.000216
DIRECT DIAL: (202) 955-1512

October 25, 1990



BY MESSENGER

Ms. Mary T. Smith
Director
Field Operations and Support Division
EN-397F
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Public Docket No. A-90-16

Dear Ms. Smith:

In comments filed with EPA on October 19, 1990, Ethyl specifically addressed two questions which arose during recent meetings with EPA officials concerning Ethyl Corporation's ("Ethyl") waiver application for use of HiTEC® 3000 ("the Additive") in unleaded gasoline. In this letter, Ethyl provides additional information relevant to one of those questions -- whether the inhalation of manganese presents risks to public-health different and more serious than those associated with the ingestion of manganese.

Enclosed for your review is a description of a model for predicting the relative share of blood manganese levels attributable to inhaled versus ingested manganese at various average ambient manganese concentrations. The model is based on human blood and circulation data, and assumptions regarding the body's absorption and excretion mechanisms governing manganese.

Application of this model shows that the contribution of inhaled manganese resulting from use of the Additive to levels of manganese in the blood would be very small. Assuming an average ambient manganese level of 0.1 ug/m3 -- a level approximately two times higher than Ethyl's worst-case prediction -- the contribution of inhaled manganese to total manganese levels in blood would be less than one percent. Under a more realistic average ambient manganese level of 0.05 ug/m3, the contribution

of inhaled manganese to blood manganese levels drops to 0.5 percent or less. This analysis demonstrates that the overwhelming source of manganese in blood, and therefore the manganese transported to the brain and other internal organs would continue to be ingested manganese even if the Additive were present in unleaded gasoline.

Sincerely,

John J. Adams
F. William Brownell
Kevin L. Fast

Enclosure

cc: Public Docket No. A-90-16
William G. Rosenberg, Esq.
Erich W. Bretthauer
Dr. J. Clarence Davies

Health Effects of Manganese in the Air

By: Ben F. Fort, Jr.
Nancy A. O'Malley

The major pathway for manganese entrance to the body is absorption in the intestines from food and water. The only other significant pathway for manganese to enter the body is from inhalation of air containing manganese particulates. However, even before considering absorption differences, the amount of manganese inhaled with air is normally much smaller than the amount taken into the gut.

A. Sources of Manganese

1. Gut Absorption of Manganese

Absorption of manganese from the human gut has been estimated by Mena et al., 1969, as 3% of oral intake for healthy subjects and 4% for manganese miners with chronic manganism. These values appear true for other mammalian species (Pollack et al., 1965).

Dietary manganese intake has been estimated as follows (EPA HAD, 1984):

Group	Average daily intake milligrams	Reference
Adults, college women	3.7 mg	North et al., 1960
Adults	2.3-2.4	Schroeder, 1966
Adults, male	3.3-5.5	Tipton, 1969
Adolescent males (15-18 years)	3.8	US FDA, 1978
Calculated average	3.05 mg	—

2. Lung Absorption

The degree of absorption of manganese from a human inhalation exposure is highly dependent upon particle size. Site of deposition and time of clearance from the site can be thought of as follows:

>10-15 um: deposited outside the thorax, insolubles cleared to esophagus and swallowed in minutes

4-10 um: 50% are deposited in the tracheobronchial tree, and are cleared on the order of hours

2-4 um: 25-65% deposited in alveoli, insolubles cleared in weeks, months, years

< 2 um:
a. 50-80% can remain suspended and be exhaled
b. Conservatively, none could be exhaled, 80% deposited alveolarly, insolubles cleared weeks, months, years

Thus, particulates deposited outside the thorax and in the tracheobronchial tree would be cleared to the gastrointestinal tract, and would be absorbed similar to dietary manganese. Dissolution of particulates in the alveoli could allow manganese to be absorbed into the lung circulation directly. Indirectly, particles could be transported to the regional lymph nodes, where dissolution could release manganese to the lymph or blood circulation. Studies of retention in man and animals have shown rapid clearance of the nasopharyngeal and tracheobronchial region, and clearance of the alveolar region dominated by the solubility of the material (Hobbs and McClellan, 1986).

The EPA in it's "Health Assessment Document for Manganese", 1984, used ambient air sampling data (NASN) to estimate human exposure by inhalation at different concentrations of air manganese. They used the air monitoring data by making the assumption that the fine fraction of particles in the air samplers would reflect particles deposited 100% in the alveoli, and the coarse fraction would represent that deposited 100% in the tracheobronchial tree. Very large particles were excluded from the samplers, and thus did not enter into their estimates. Total thoracic exposure would be particles deposited in the alveoli and in the tracheobronchial tree.

The following exposure estimates were made by the EPA for a 70 kg man breathing 20 cubic meters (m^3) of air per day:

NASN data used	Concentration (ug/m^3)	Total inhaled Mn, ug/day*	Site Deposited	Exposure (ug/day)
1982 avg.	.023	.460		
			alveolus	.072
			total thoracic	.26
1982 high	.661	13.22		
			alveolus	6.6
			total thoracic	10.0
1960 high	10	200.00		
			alveolus	100
			total thoracic	152

(From EPA HAD, 1984 except for * which was calculated from air concentration)

(Tracheobronchial manganese = Total thoracic - alveolar manganese)

B. Possible differences in inhaled versus ingested manganese

There has been speculation that manganese in the blood resulting from lung absorption might increase significantly before it is regulated by the body control mechanisms for manganese coming from dietary sources. This is based on possible differences in elimination mechanisms for manganese in the blood originating from lung or from gut absorption. Manganese absorbed via the gut into venous blood flows through the liver where the liver elimination mechanisms regulate the blood concentration before circulation to other body tissue and organs. Manganese absorbed into blood in the lung enters arterial blood directly and is circulated to body tissue and organs. Only about 21% of the total venous blood flows through the liver each blood flow cycle. The 79% venous blood that does not pass through the liver is an internal loop which provides the possibility of buildup of lung-absorbed manganese.

C. Blood Flow Model

To examine the relationships of air and gut manganese to the circulating manganese levels, a simple model of body blood flow was constructed. The model is capable of evaluating the relative fractions of blood manganese originating from lung and gut absorption as the inhaled air manganese content varies. The fractions are evaluated at homeostatic-regulated total blood manganese content.

The complete blood flow system is depicted in Figure 1. All major body organs and systems are shown with the generally accepted percentages of total blood flow (Guyton, 1987; Ritschel, 1976). The major manganese inputs are absorption from the gut and lung represented in Figure 1 by the MnG and MnI variables, respectively. The minor input from skin absorption is not considered. Manganese is eliminated from the body in feces, bile, fingernails and toenails, urine and hair. The urine elimination route is thought to become active only after the liver route is overwhelmed. The bile and feces are the only routes of elimination considered in the model at this time.

The computations in the model are iterative with respect to air/gut ratio in the blood and liver elimination fraction. The air/gut ratio is a direct solution for fixed elimination fraction but was programmed as iterative to retain the generality of the solution technique. The homeostatic regulation of total blood manganese flow was achieved by iterative adjustment of the liver elimination fraction. This type model can be utilized for an enhanced model involving sources and/or sinks plus time dependent functions affecting these sources and/or sinks. The computed air/gut ratios for various levels of air concentrations will be discussed in Section E following.

D. Assumptions and Parameters for the Model

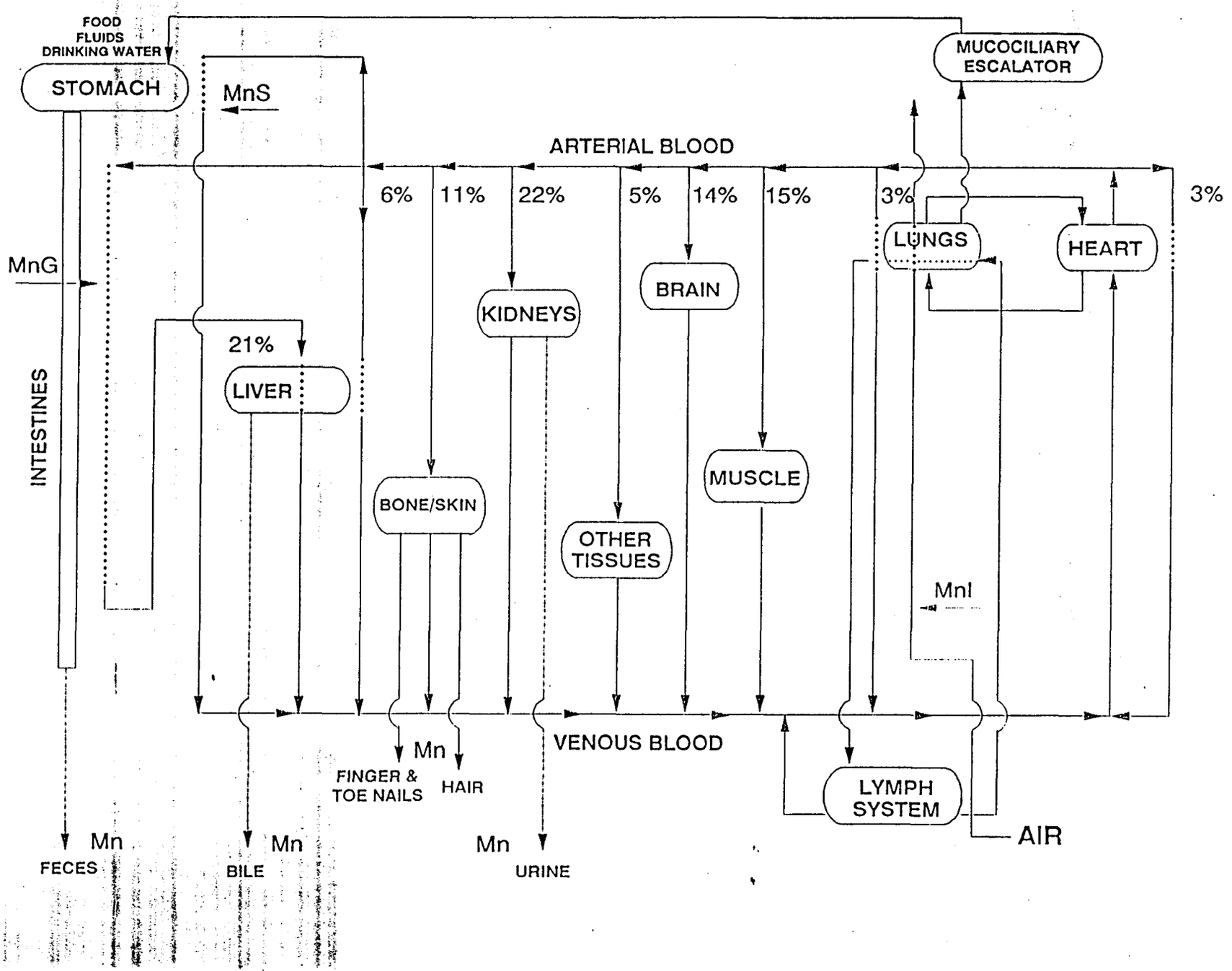
The model input parameters are based on human blood and circulation data. Blood manganese content from the literature exhibits a wide range of values. Factors altering blood values can include tissue fluid contamination in sampling whole blood, the analytical method used and the choice of anticoagulant. The EPA "Health Assessment Document for Manganese", 1984, states neutron activation and electrothermal atomic absorption analytic procedures have shown average normal concentrations of manganese in whole blood to be 0.7-1.2 ug/100 ml.

Our model assumed that the blood manganese levels would be tightly controlled by the body absorption and excretion mechanisms. This is supported by animal studies. Ulrich's study (1979) in which squirrel monkeys and rats were exposed continually by aerosol for 9 months to 11.6, 112.5 and 1152 ug Mn/m^3 with particles of 0.11 um diameter did not show significant elevations of blood manganese except at the highest exposure level.

Exposure Group (ug/m^3)	Rats (n=10) (ug/100 ml)	Monkeys (n=4) (ug/100 ml)
Control	1.15 +/- 0.46	1.10 +/- 0.17
11.6	1.30 +/- 0.55	1.30 +/- 0.13
112.5	1.75+/- 1.06	1.54 +/- 0.17
1152	2.43 +/- 0.88	5.67 +/- 1.28

Figure 1

Human Blood Flow System



As our model was going to consider concentrations well below 1152 ug/m^3, we assumed that blood concentrations would be controlled at steady state to preexposure values. For modelling, a blood concentration of 1.2 ug/100 ml was used. At a flow rate of 5000 ml/minute, a manganese flow of 60 ug/minute resulted and was assumed to originate from gut absorption.

Dietary intake has definite influence on manganese clearance rates. For example, Britton and Cotzias (1966) reported a two-component whole body clearance rate for manganese in mice. A 10 fold increase in dietary intake decreased the half time of the isotope by about 50%. Suzuki (1974) had similar findings in a study in mice receiving different levels of manganese in drinking water for 30 days before radiolabel. Whole body clearance was estimated to be 6 days for lowest concentration group (20 mg/l), and decreased to 3 days (100 mg/l) and 1 day (2000 mg/l). Our model can vary dietary intake values for manganese, but for the present discussion, dietary levels were kept at an average daily intake of 3.05 mg/day (EPA HAD, 1984).

A 70 kg man inhales approximately 20 cubic meters of air per day (EPA HAD, 1984). While all the manganese in this air would be inhaled, studies of particulate distribution show that only approximately 16% of it would be distributed such that it could be absorbed into the bloodstream (Yeh and Scham, 1980). Thus, the model initially used the assumption that 16% of inhaled manganese would be absorbed. (Sixteen per cent absorption of inhaled manganese is comparable to the absorption calculated from the estimated alveolar exposure of a 70 kg man at an air concentration of 0.023 ug/m^3 as developed in the EPA HAD, 1984. This is shown below.) The lung absorption was made variable in the model and can be increased or decreased to reflect changes in the overall absorptivity (particle distribution and solubility) of the inhaled manganese. (The same effect on blood levels could be realized by artificially increasing the air concentration.) Values of 50% lung absorption appear to fit the higher ambient air concentrations in the EPA exposure estimate.

NASN data used	Air levels (ug/m^3)	Mn in 20m^3 ug/day*	Alveolar exposure (ug/day)	Absorption*
1982 avg.	.023	.460	.072	16%
1982 high	.661	13.22	6.6	51%
1960 high	10	200.00	100	50%

(From EPA HAD, 1984 except for * which was calculated from air concentrations, and the alveolar absorption estimate)

By adjusting the manganese lung absorption variable in the 20 to 45 percent range, the model produces very comparable air/gut contribution to blood manganese ratios to those that can be derived from the data used for exposure estimates in the EPA HAD, 1984.

E. Comparison with estimates derived from the EPA Exposure Estimates

From the EPA estimates of exposure, the relative contribution of inhaled and ingested manganese to the circulating manganese can be approximated. Using the very conservative assumption that all manganese in the alveolus is absorbed into the blood during the day it is inhaled, and that tracheobronchial manganese would be carried to the esophagus and swallowed, the distribution of the inhaled manganese (from the same ambient air concentrations) would be:

Air concentration ug/m^3	Amt Mn into blood from Alveolus	Amt Mn into gut from Lung
.023	+ .072 ug/day	+ .188 ug
.661	+ 6.6 ug/day	+ 3.4 ug
10	+100 ug/day	+ 52 ug

Carrying the EPA estimates a step further, contributions to circulating manganese can be estimated from dietary intake. Daily ingested manganese averages 3.05 mg/day (average value for healthy adults, EPA, 1984). Tracheobronchial manganese is also delivered to the gut. Absorption of gut manganese is approximately 3% (EPA, 1984). The intake of manganese from the lung (alveolus) into the blood, and from the gut (diet and tracheobronchial) into the blood can be estimated as:

Air ug/m^3	Intake from lung	Intake from gut	Air/gut %	Air/Total Intake%
.023	.072 ug/day	91.51 ug	.079%	.078%
.661	6.6 ug/day	91.60 ug	7.2%	6.7%
10	100 ug/day	93.06 ug	107.4%	51.8%

Our blood flow model, using a blood manganese level of 1.2 ug/100 ml, the same 3.05 mg Mn in the diet, shows very similar air gut and air total ratios at steady state letting lung absorption vary from 20-45%, as shown below:

Air ug/m^3	Air/gut %	Air/Total Intake%
0.023	0.10-0.23% (.079% EPA)	0.10-0.23% (.078% EPA)
0.05	0.22-0.49%	0.22-0.49%
0.1	0.44-0.99%	0.44-0.98%
0.661	2.90-6.53% (7.2% EPA)	2.82-6.13% (6.7% EPA)
10	43.97-99.14% (107.4% EPA)	30.54-49.78% (51.8% EPA)

Note: Minimum value assumes 20% lung absorption.
Maximum value assumes 45% lung absorption.
EPA value is calculated from EPA HAD, 1984 data.

Similarly, the model was used to estimate air/ingestion contribution ratios using the Human Equivalent Exposure Levels (HEEL) estimated from animal data by the EPA, 1984. The HEEL values were derived from the no observed effect levels seen in two species of animals in an inhalation study by Ulrich et al., 1979. The no observed effect levels were 113 ug/m^3 for 9 months of continual exposure in rats and squirrel monkeys. Using size factors to estimate animal intake and making adjustments for human proportions, and applying a safety factor of 10 to the estimated human equivalent exposure level, the adjusted air concentrations were 5 and 8.7 ug/m^3 based on the rat and squirrel monkey data. The contribution ratios calculated by our model for this air concentration, using 45% absorption for inhaled manganese are as follows:

Air ug/m^3	Air/gut %	Air/Total Intake%
5	49.47%	33.10%
8.7	83.80%	46.30%

Note: Values assume 45% absorption
Air concentrations are Modified HEEL values, EPA HAD, 1984

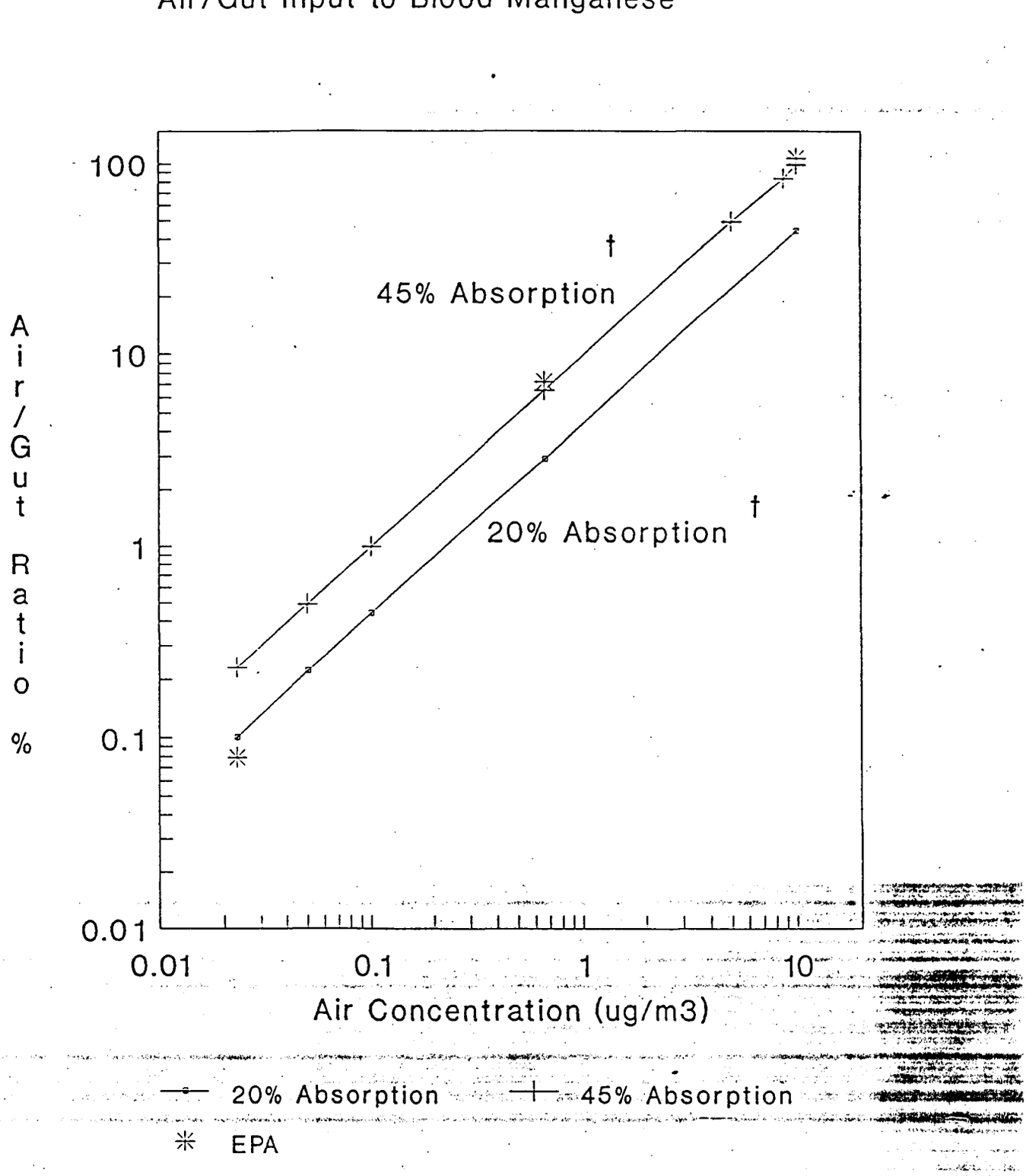
These results for air/gut ratios at different air concentrations are plotted in Figure 2. As has been mentioned, the model reasonably approximates the air/gut contributions to blood manganese at homeostasis derived from the EPA estimates of alveolar exposure at air concentrations that vary from 0.023 to 10 ug/m^3. Even assuming 45% lung absorption in our model (an absorption value that better fits very high air concentrations rather than the 16-20% that better fits low concentrations), the air/gut ratios for the air concentrations of concern (less than 0.1 ug/m^3) are 1% or less.

Based on this model, using a conservative assumption that 45% lung absorption of manganese from ambient air containing 0.1 ug/m^3 would occur and that dietary intake of manganese would be 3,050-3,500 ug/day (an average dietary intake to the recommended daily allowance, NRC, 1989), only 1% by weight of blood manganese would be attributable to inhaled manganese at steady state. If a more realistic average air concentration of manganese of 0.05 ug/m^3 is used, the amount of blood manganese attributable to inhalation drops to 0.5%.

Conclusions:

Based on calculations from this model, we conclude that at average current ambient air manganese concentrations -- and at maximum ambient manganese concentrations that will result from the proposed use of HiTEC® 3000 (conservatively predicted to be approximately 0.05 ug/m^3) -- manganese from inhalation constitutes less than one percent of the blood manganese. Air is therefore the source of less than 1% of the manganese reaching the brain at homeostasis. (In comparison, air/gut ratios of 49-84% would be seen at air concentrations that are the human equivalents of no effect exposures in animals.)

Figure 2



† Percentage of inhaled manganese which is absorbed.

REFERENCES:

Bethard, W.F., Olehy, D.A., and Schmitt, R.A. 1964. "The use of neutron activation analysis for the quantitation of selected cations in human blood. In: L'analyse per Radioactivation et les Aplications aux Sciences Biologiques. III. Colloque International de Biologie de Saclay. Sept. 1963. Presses Univ. France, Paris. p. 379-393.

Britton, A.A. and Cotzias, G.C. 1966. "Dependence of manganese turnover on intake." Am. J. Physiol. 211(1): 203-206.

Coulston, F. and Griffon, T. 1976, "Inhalation Toxicology of Airborne Particulate Manganese in Rhesus Monkeys," Contract 68-02-0710, Albany Medical College, Holloman Air Force Base, New Mexico.

Guyton, A.C. 1987. Textbook of Human Physiology, W.B. Saunders, Philadelphia.

Hobbs, C.H., and McClellan, R.O. 1986. "Deposition, Retention, and Responses to Inhaled Materials," In Safety Evaluation of Drugs and Chemicals, Ed. W.E. Lloyd. Hemisphere Publishing Corporation, New York, New York. pp. 285-304.

Mena, I., Horiuchi, K., Burke, K., and Cotzias, G.C. 1969. "Chronic manganese poisoning: Clinical picture and manganese turnover." Neurology, 19: 1000-1006.

Newland, M.C., Cox, C., Hamada, R., Oberdorster, G., and Weiss, B. 1987. "The Clearance of Manganese Chloride in the Primate", Fund. and App. Tox., 9, 314-328.

NRC (National Research Council). 1989. Recommended Dietary Allowances, 10th ed. Food and Nutrition Board, National Research Council, National Academy Press, Washington, D.C. p. 230-235.

Pollack, S., George, J.N., Reba, R.C., Kaufman, R.M., and Crosby, W.H. 1965. "The absorption of nonferrous metals in iron deficiency." J.Clin. Invest. 44(9): 1470-1473.

Ritschel, W.A. 1976. Handbook of Basic Pharmacokinetics, Drug Intelligence Publications, Hamilton, Illinois.

Schroeder, H.A., D.D. Balassa and I.H. Tipton. 1966. "Essential trace metals in man: Manganese, a study in homeostasis". J. Chron. Dis. 19: 545-571.

Suzuki, Y. 1974. "Studies on excessive oral intake of manganese. II. Minimum dose for manganese accumulation in mouse organs." Shikoku Acta Med. 30: 32-45.

Ulrich, C.E., Rinehart, W., Busey, W. 1979. "Evaluation of the chronic inhalation toxicity of a manganese oxide aerosol", Am Ind Hyg Assoc. J. (40) 3/79, pp 238-244.

REFERENCES (Continued)

Ulrich, C.E., Rinehart, W., Busey, W. 1979. Evaluation of the chronic inhalation toxicity of a manganese oxide aerosol, Am Ind Hyg Assoc. J(40) 4/79, pp 322-329.

Ulrich, C.E., Rinehart, W., Busey, W. 1979. Evaluation of the chronic inhalation toxicity of a manganese oxide aerosol, Am Ind Hyg Assoc. J(40) 5/79, pp 349-353.

WHO (World Health Organization). 1973. "Trace elements in human nutrition: Manganese." Report of a WHO Expert Committee. Technical Report Service, 532, WHO, Geneva, Switzerland. pp. 34-36.

Yeh, H.C. and Scham, G.M. 1980. Models of human lung airways and their application to inhaled particle deposition. Bull. Math. Biol. 42, 461-480.

U.S. EPA, 1984. "Health Assessment Document for Manganese," PB84-229954.